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EPILEPSY

ABSTRACT & COMMENTARY

Mozart Therapy for Epilepsy

By Nancy Selfridge, MD

Dr. Selfridge is Professor, Clinical Foundations Department, Ross University School of Medicine, Barbados, West Indies

Dr. Selfridge reports no financial relationships relevant to this field of study.

SYNOPSIS: A randomized, controlled, crossover trial in adult patients with drug-resistant epilepsy compared listening to a Mozart piano sonata daily to an active control. It showed reduction in seizures during the Mozart treatment compared to both baseline and the control treatment.

SOURCE: Rafiee M, Patel K, Groppe DM, et al. Daily listening to Mozart reduces seizures in individuals with epilepsy: A randomized control study. *Epilepsia Open* 2020;5:285-294.

The "Mozart Effect" was coined after a 1993 publication in *Nature* reported temporary improvement in spatial task performance by college subjects after exposure to brief periods of listening to a Mozart sonata for two pianos ("K.448").[1] Since then, many studies have investigated the "Mozart Effect" as a potential intervention for cognitive disorders, mood disorders, and other psychiatric diagnoses, as well as neurologic disorders.[2]

A 1998 publication by Hughes et al documented significant seizure and electroencephalogram epileptiform activity reduction in patients with epilepsy listening to Mozart "K.448," even in status epilepticus and coma. A similar therapeutic effect was not associated with listening to a pop piano piece.[3]

This work subsequently inspired significant research activity evaluating this Mozart piece therapeutically for refractory epilepsy. In 2014 and 2018, systematic reviews of studies over the previous 15 to 20 years investigated the efficacy of Mozart as a treatment tool for epilepsy. They concluded that a therapeutic effect appeared likely, but studies to date had been hampered by methodologic flaws, the most common of which was lack of an active control.[4,5] It makes sense that any control condition other than an al-

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Summary Points

- Music therapy — represented primarily by daily listening to Mozart's "K.448" — has been shown in several studies to reduce seizure frequency in both adult and pediatric patients with drug-resistant epilepsy, although studies have been hampered by methodologic flaws.
- In this well-constructed randomized controlled trial with a crossover design, patients with drug -resistant epilepsy listened daily to either Mozart "K.448" or a cleverly constructed, non-rhythmic audio control, recording seizure frequency in a diary.
- Seizures were reduced significantly in the Mozart treatment group compared to both baseline, pre-study seizure experience and during the control exposure period in both intention-to-treat and per-protocol analyses.

ternative style or piece of music would be challenging.

In this well-designed study, investigators implemented a randomized, controlled, crossover trial that addressed some of the methodologic flaws of the previous work. Based on its consistent application in extant research, Mozart's "K.448" was chosen as the active treatment. Researchers then created an active control from the same musical piece, subjected to phase-scrambling that preserved the auditory frequency and amplitudes of "K.448" but without any rhythmicity.

The auditory interventions were limited to the first "allegro con spirito" movement (six minutes) of "K.448" (24 total minutes) for practical purposes. They hypothesized that there would be no difference in seizure frequency between active treatment and control periods. Participants were selected from adult patients with epilepsy previously admitted to an epilepsy monitoring unit at Toronto Western Hospital. Inclusion criteria consisted of:

- dissatisfaction with seizure control despite drug therapy;
- at least three seizures in the three-month "baseline" period preceding the study and at least one seizure within the past two months.

Exclusion criteria were extensive and included:

- any history of brain resection surgery;
- any changes in seizure medication during the one-year study period;
- use of vagus nerve or deep brain stimulation or a ketogenic diet at the time of enrollment or during the study period;
- inability to recall or document seizure episodes in a diary;
- inability to understand or speak English;
- a score of less than 55% on a pitch perception and hearing impairment online test administered prior to starting the intervention.

Of 1,107 subjects assessed for eligibility, 13 met study inclusion criteria and were randomized to either Group A (7 participants) or Groups B (6 participants). After a baseline period of three months, allowing documentation of seizure occurrence, Group A and B began treatment. Both groups experienced three months of once-daily Mozart listening and three months of "scrambled" Mozart listening; Group A began with the Mozart piece and Group B began with the "scrambled" control. After three months, the groups switched interventions.

A three-month follow-up period allowed subjects to assess seizure control after the six months of interventions. Subjects documented seizures in a diary throughout the one-year study period. Auditory files for the interventions could be accessed via a password-protected website that also would prompt subjects to complete a survey question after listening, allowing some assessment of adherence.

Subjects who did not choose to use the website for access to audio files were provided an electronic copy of the sound files and then requested to indicate any missed

days of listening in their diaries. Primary outcome was seizure frequency as indicated by diary entries.

Two subjects from Group A dropped out of the study, one because of a change of medication and one because of dissatisfaction with seizure control during the control intervention. Therefore, results included both per-protocol and intention-to-treat analyses of data. Baseline period seizure numbers for each subject were used to normalize paired observations of recorded seizures during the treatment and control periods. Effects sizes were calculated from mean differences between these normalized, paired observations.

Results are summarized in Table 1. Seizure count was reduced for subjects in both groups during the treatment period compared to control period for both intention-to-treat analysis (-44% for Group A, -25% for Group B) and per-protocol analysis (-59% for Group A, -25% for Group B). Paired *t* tests confirmed a significant treatment effect and Cohen's *d* values indicated a large effect size (> 0.8). An average 35% reduction in seizure counts resulted from daily listening to Mozart's "K.448" compared to listening to a scrambled version, devoid of any rhythmicity, of the same piece.

■ COMMENTARY

A significant strength of this study is that it addresses the absence of an active control present in previously published, quasi-experimental study designs. The sample size was ultimately small because of the numerous exclusion criteria, but the crossover design allowed valid statistical inferences that could not be made in a parallel study design with so few subjects. The intervention certainly was reasonable and manageable, supported by high compliance rates (83 ± 11% and 72 ± 16% for treatment and control periods, respectively).

The authors suggested that the lack of a washout period between treatment and control periods ignores a potential carryover effect and represents a weakness of the study that should be addressed in future research, along with optimum treatment time and "dosing" for maximum and/or sustained effect.

[... the cleverly scrambled "K.448" control employed by Rafiee et al suggests that the therapeutic effect of listening to Mozart "K.448" is not exclusively due to sound frequencies and amplitudes, which were identical in this study's treatment and control interventions — a noteworthy contribution to this debate.]

Experts continue to debate what element of the musical intervention is responsible for its positive therapeutic effect. Hypotheses include a parasympathetic effect from perceived pleasurable experience, brain wave entrainment caused by specific sound frequencies and amplitudes, or physiologic changes induced by auditory rhythms.[2] Interestingly, despite the proposed hypothesis that the therapeutic effect attributed to this Mozart piece may be the result of physiologic effects of listening to pleasurable music in general, similar therapeutic effects for other musical pieces has not been found, except for one other Mozart piano sonata ("K.545").[6,7]

Some experts have continued to argue that the nearly universal human experience of Mozart compositions as pleasing may yet explain the therapeutic effect of this music. However, a study of rats demonstrated improved maze running performance when exposed

Table 1. Summary of Results*

	Intention-to-Treat Analysis		Per-Protocol Analysis	
	Group A (n = 7)	**Group B (n = 6)**	**Group A (n = 5)**	**Group B (n = 6)**
Mean seizure count reduction (treatment period compared to control period)	-44%	-25%	-59%	-25%
Treatment effect (paired *t* test results)	*P* value = 0.0005 *t* value = 4.75		*P* value = 0.0009 *t* value = 4.61	
Paired Cohen's *d* (95% confidence interval)	1.5 (0.7 to 2.1)		1.6 (0.7 to 2.5)	

*Compliance rates: Group A 83 ± 11%; Group B 72 ± 16%

to Mozart "K.448," whereas no improvement in maze running occurred when these rats were similarly exposed to Beethoven's "Für Elise," suggesting that Mozart's works are unique in this regard.[8]

Is brain activity then "entrained" by the specific sound frequencies in these Mozart works? One study noted a seizure-reducing effect of the "K.448" piano piece that was not noted for a string version of the same piece, suggesting a therapeutic effect because of sound frequencies.[9]

However, the cleverly scrambled "K.448" control employed by Rafiee et al suggests that the therapeutic effect of listening to Mozart's "K.448" is not exclusively the result of sound frequencies and amplitudes, which were identical in this study's treatment and control interventions — a noteworthy contribution to this debate.

In summary, based on the positive results reported in this study and while awaiting further research, practicing clinicians can consider recommending this no-cost/no-risk intervention to patients with epilepsy who are not content with their seizure control on prescribed medication. ■

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PAIN

ABSTRACT & COMMENTARY

Scrambler Therapy for Neuromyelitis Optica Pain Treatment

By Lindsey N. Clark, MD, and Nancy J. Selfridge, MD

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Dr. Clark and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: Scrambler therapy appears to significantly reduce central neuropathic pain for patients with neuromyelitis optica spectrum disorder, although pain reduction is not shown to be sustained for more than 30 days after treatment.

SOURCE: Mealy MA, Kozachik SL, Cook LJ, et al. Scrambler therapy improves pain in neuromyelitis optica: A randomized controlled trial. *Neurology* 2020;94:e1900-e1907.

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune, inflammatory disorder of the central nervous system. Diagnosis is based on the presence of an NMO-IgG autoantibody that attacks the aquaporin-4 water channel on the feet of astrocytes in the central nervous system, resulting in demyelination, axonal damage, and axonal loss in the optic nerves and spinal cord.

Patients subsequently experience repeated episodes of optic neuritis and transverse myelitis throughout the course of the disease, manifesting as uncontrolled pain. Previous studies report that more than 80% of patients with NMOSD experience pain that severely affects their quality of life.[1] Both spastic and neuropathic pain are present in NMOSD patients, with the latter reported as more common and difficult to control.[2] Common current agents for treatment include antiepileptics, antispasmodics, antidepressants, and analgesics, yet often lack immediate relief and long-term efficacy for NMOSD-associated central neuropathic pain.[1]

Summary Points

- In this randomized controlled trial to study the effectiveness of scrambler therapy for pain treatment in patients with neuromyelitis optica, 22 patients completed the study — 11 each in a scrambler therapy arm and an active control arm.
- Pain scores decreased from 5.0 to 1.5 on a numeric rating scale after 10 days of scrambler therapy. There was no significant decrease in the sham arm. Therapeutic effects were sustained at a 30-day follow-up, but not at 60-day follow-up.
- Patients receiving scrambler therapy also reported decreases in anxiety and depression, with a significant decrease in depressive symptoms.

Scrambler therapy has been studied and used as a treatment for persistent peripheral neuropathic pain, as seen postsurgically, in chemotherapy-induced neuropathy and in postherpetic neuralgia. Prior to this study, only two case reports described benefits of scrambler therapy in NMOSD patients, and there were no randomized controlled trials of this intervention for patients suffering central neuropathic pain.[3]

The scrambler therapy device consists of five artificial neurons controlled by an optimized algorithm that creates "non-pain" signals, which can be transmitted along C-fibers, ultimately leading to diminished pain sensations in the brain.[4] A typical scrambler therapy regimen is 10 to 12 consecutive treatments performed over a two-week period.

In this study, the authors used a randomized, experimental design with an active placebo control. Twenty-three patients were assessed for eligibility, resulting in 22 patients (11 per arm) enrolled at Johns Hopkins Neuromyelitis Optica Clinic. One patient declined to participate.

Inclusion criteria consisted of neuropathic pain attributed to inflammatory lesions of the spinal cord, indicated on magnetic resonance imaging and persistent pain (present for more than three months) rated > 4 on an 11-point numeric rating scale (NRS).

Exclusion criteria consisted of concomitant diagnosis of peripheral neuropathy or ongoing central neurologic disorder and use of investigational pain agents within 30 days of enrollment. Patients were randomly assigned to receive either scrambler therapy or sham treatment.

The scrambler therapy device used in the study was the GEOMC Pain Scrambler model MC-5A (Seoul, South Korea). A single, trained technician administered all scrambler therapy sessions as well as sham regimens, creating a single-blinded study design. Participants receiving scrambler therapy had electrodes placed in dermatome areas above and below the level of their spinal lesion, close to their pain. The signal intensity was increased to a maximum threshold for each participant. Then, the electric signal was adjusted to create an analgesic effect in the area of pain and applied for 35 minutes for each session. Participants in the sham group were connected to electrodes that produced vibratory sensations similar to scrambler stimulation. However, no electrical signals were transmitted for participants in the control group.

The scrambler therapy device and sham equipment were kept behind a curtain, thus masked from participants. An unrelated, blinded study coordinator collected all measurements and survey data to mitigate bias.

[Scrambler therapy ... appears to have no significant adverse effects and, thus, presents a safer alternative to these prescription drugs and may yield greater pain relief effectiveness.]

Brief Pain Inventory (BPI) and Quality of Life in Neurological Disorder (Neuro-QoL) Short Form versions 1.0 were used to assess patient baseline pain and co-occurring conditions, including anxiety, depression, and sleep disturbance. Effectiveness was defined as degree of improvement from baseline pain and compared between the study group and the control groups using Friedman one-way repeated measure analysis of variance. Subjects were tested immediately after treatment and at 30-day and 60-day follow-up. Wilcoxon signed-rank testing was used to determine the sustainability of pain improvement by comparing pain scores at 30-day and 60-day follow-ups.

With the study participant size of 11 participants per arm, Mealy et al report a study power of 80%, with a 60% difference in proportion between the two arms.

The co-occurring symptoms (anxiety, depression, and sleep disturbance) were analyzed similarly to pain via Friedman one-way repeated measure. Demographic and clinical characteristics were compared between scrambler and sham groups by use of Mann-Whitney U and X^2 testing.

Twenty-two participants completed the treatment and sham regimens. Results from the study provided Class II evidence of scrambler therapy use in patients with NMOSD. No serious adverse events were reported during the study. Results showed a majority of participants were female (91%) and Black (59%), consistent with the general NMOSD population. All participants were seropositive for the NMO-antibody (Anti-aquaporin-4 antibody). X^2 analysis showed the masking technique was successful, with no difference between the two groups in patients who believed they had received scrambler therapy.

The baseline pain level for all participants in the study was 5.0 on NRS scale. Immediate pain measurement after scrambler therapy showed a significant reduction in NRS pain score from 5.0 to 1.5 ($P = 0.001$), whereas the sham group showed a reduction in NRS pain score from 5.0 to 4.0 ($P = 0.4239$). (*See Table 1.*) Additionally, the scrambler therapy group showed significantly decreased pain at the 30-day post-intervention measurement ($P = 0.0195$) that was not sustained at the 60-day measurement.

Depression was the only co-occurring symptom to be significantly reduced after treatment with scrambler therapy ($P = 0.03$). No significant decrease was detected in anxiety ($P = 0.10$) or sleep disturbance ($P = 0.26$). In the sham arm, there was no significant change in depression, anxiety, or sleep disturbance immediately after the study, nor at the 30-day and 60-day mark.

■ COMMENTARY

This well-designed study presents evidence supporting the effectiveness of scrambler therapy for the treatment of central neuropathic pain in NMOSD patients and contributes to developing theories that the "non-pain" signals generated by the scrambler therapy device serve to displace and modify pain signals generated both in the peripheral and central nervous systems.[4] Ultimately, it appears the brain is being rewired to receive "non-pain" messages, creating an analgesic effect. Mealy et al have shown that scrambler therapy can successfully be studied in a randomized experimental setting using a masking technique and a clever sham simulation therapy that allows comparison and control for the placebo effect.

Scrambler therapy appears to be an effective pain treatment option for a patient population that appears to experience more frequent and intense pain when compared to other autoimmune demyelinating diseases, such as multiple sclerosis (MS). Multiple studies of pain in NMOSD cases indicate pain is a major complaint for more than 80% of patients, whereas 47% of patients with MS report pain as a major concern.[5] Additionally, patients with NMOSD report significantly higher pain severity levels and experience greater life disruption because of pain than patients with MS, and pain is reported as an overlooked symptom as physicians work to address the many other debilitating symptoms of NMOSD.[5,6,7]

Considering that the current pain treatment regimens for NMOSD patients involve antiepileptics, antispasmodics, antidepressants, and opioid analgesics, NMOSD patients often are put at risk for unwanted side effects, including tolerance, drowsiness, sedation, and weakness.[1] Additionally, NMOSD patients are more likely than MS patients to experience high prevalence of use of pain medications with a lower percentage of pain relief.

In a recent (2020) study by Hyun et al studying pain experiences in NMOSD and MS patients, NMOSD patients reported significantly greater unsatisfactory pain relief than MS patients (38% vs. 13%, $P = 0.031$) combined with a higher frequency of pain medication use (82% vs. 60%, $P = 0.46$) and overall lower pain relief (50% vs. 60%, $P = 0.037$).[8] Scrambler therapy, in contrast, appears to have no significant adverse effects and, thus, presents a safer alternative to these prescription drugs and may yield greater pain relief effectiveness.

Even though scrambler therapy may be an effective way to treat pain in NMOSD patients, initial results from this study showed a sustained reduction in pain

Table 1. Scrambler Therapy vs. Control

Scrambler Therapy			**Control Group**		
Baseline median NRS pain rating	Immediate NRS pain rating (10-day post)	*P* value	Baseline median NRS pain rating	Immediate NRS pain rating (10-day post)	*P* value
5.0 (2.8)	1.5	$P < 0.0001$	5.0 (3.2)	4.0	$P = 0.4239$

NRS: numeric rating scale

only at the 30-day follow-up. The authors noted a lack of sustained pain improvement in study participants receiving scrambler therapy at the 60-day follow-up, which may be explained by a lack of statistical power with the low number of subjects in this study.

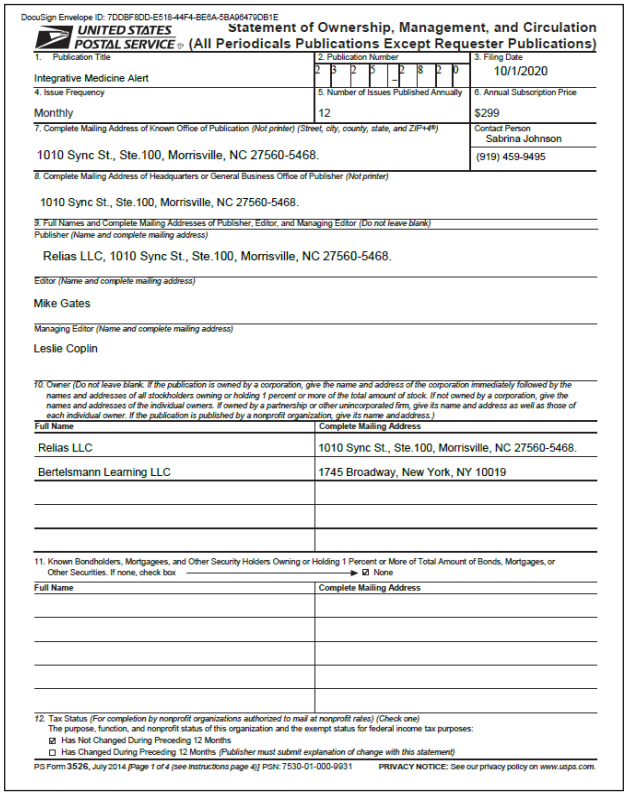
The authors noted that an enrollment of 29 patients per arm would be required to give a similarly devised study the power to detect a significant change at 60 days post-treatment. Further work should include larger study populations with the power to detect the ability of scrambler therapy to induce long-term pain reduction in patients with central neuropathic pain.

While awaiting further studies, scrambler therapy can be recommended to patients with neuropathic pain as a safe, alternative treatment that may provide at least a few months of relief for most patients.

Recent estimates report an average cost of a scrambler therapy session costing $200 to $500 per session in cancer pain therapy programs, where it is used more widely.[9,10] Insurance coverage for sessions is variable among insurance companies, with many patients opting to pay in cash.

However, in 2014, a federal ruling stating that scrambler therapy is effective and should be covered under Medicare may lead to more cost-effective and wider treatment availability for patients.[11] Many insurance providers continue to cite insufficient evidence regarding effectiveness as the primary reason for lack of coverage.[12,13]

Future studies using a randomized control design, such as Mealy et al, to study scrambler therapy for central neuropathic pain relief are necessary to build a substantial body of evidence to support scrambler therapy for pain relief in NMOSD patients. ■



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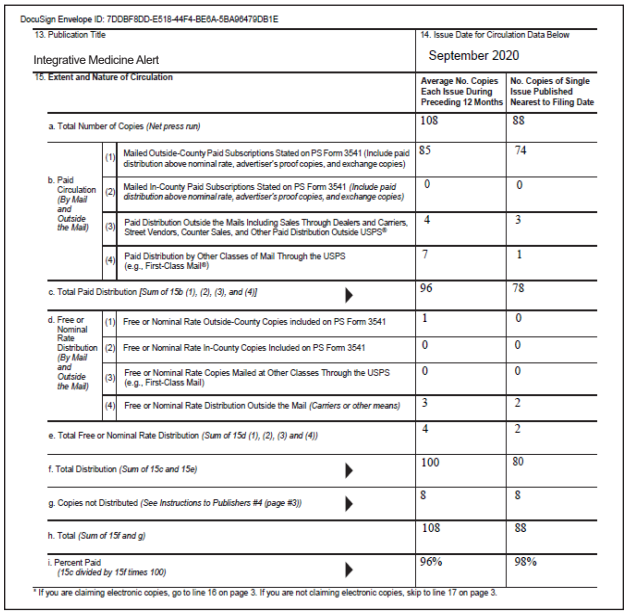

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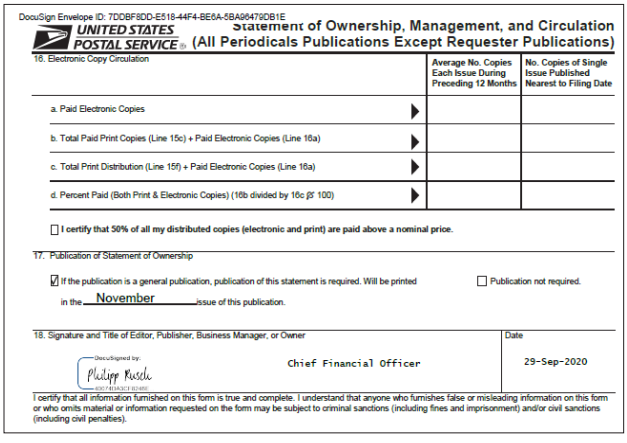

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

CME INSTRUCTIONS

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CME QUESTIONS

1. The mechanism of scrambler therapy is best described as:
a. antagonism of nociceptors.
b. presynaptic inhibition of neurotransmitter release.
c. artificial neurons that create non-pain signals, which are transmitted along C-fibers.
d. inhibiting brain activity in the dorsal posterior insula.

2. Which of the following best describes the therapeutic efficacy of listening to music for reducing seizure frequency in patients with epilepsy?
a. Sound frequency is clearly responsible for the therapeutic effect.
b. All classical music appears to have the same seizure-reducing effect.
c. Only two Mozart piano sonatas appear to reduce seizure activity.
d. Therapeutic use of listening to music is associated with low patient adherence.

[IN FUTURE ISSUES]

Long-Term Exposure to Air Pollution and Cognitive Decline

Fruits, Vegetables, and Type 2 Diabetes

Early Childhood Sleep Problems Tied to Later Mental Health Issues